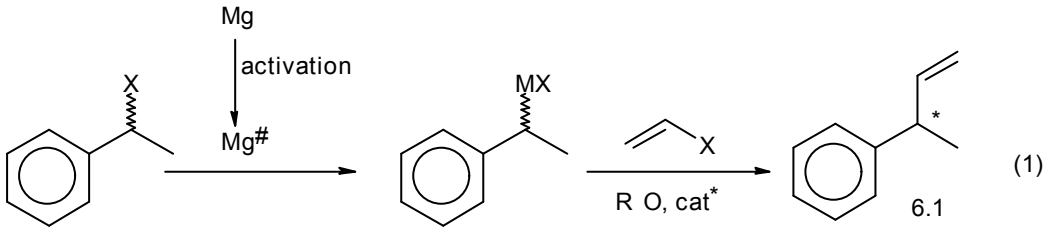
Chapter 6

Towards Enantioselective S_N2' Reactions

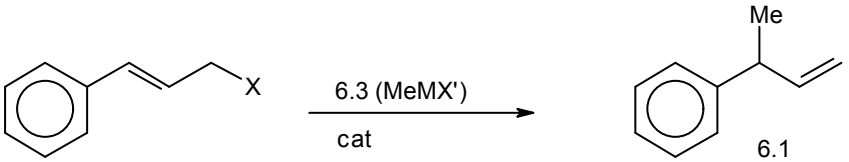
6.1 Introduction

In the first part of this thesis, we have described the asymmetric synthesis of profen precursor **6.1** by asymmetric catalysed cross coupling reactions (Chapters 2, 4, and 5). In brief, this reaction involves a stereoselective carbon–carbon bond formation between a vinylic- and a benzylic moiety, and the reaction is catalysed by a chiral, non racemic catalyst (Scheme 6.1, Eq. 1). The benzylic magnesium halide reagent is a chiral, racemic compound that appears to racemize on the same time scale as the cross coupling reaction. Therefore, the asymmetric cross coupling reaction is a dynamic kinetic resolution. We concluded from our work, as well as that of others, that the *ee* of the product depends on too many variables, some of which are beyond control. We are inclined to believe that the degree of reproducibility of the *ee* of **6.1** is a function of the specific research group and researcher. As a consequence, the asymmetric cross coupling reaction at hand is an unreliable measure to rank ligands with regard to their enantioefficacy, unless the conditions used are specified very precisely.



(1)

(Some of the factors that potentially influence the enantioselection are printed in italics)



(2)

6.2a: X = OAc
6.2b: X = Br
6.2c: X = Cl

M = Mg, Li, Zn, Cu, Ti, etcetera
X' = halide, alkyl, etcetera
cat = $Cu^{(I)}$- salt (complex)

Scheme 6.1

Further, the above mentioned complications are unacceptable for a reaction that is intended for a larger scale process. For these reasons, we looked for an alternative asymmetric catalytic process to prepare **6.1**.

Recapitulating, this research was set up within the framework of asymmetric catalysis, leading to a precursor of profen compounds like **6.1**. This has been discussed in Chapter 1. Therefore, the alternative approach we searched for had to fit in this framework as well. The alternative approach must involve asymmetric catalysis and formation of profen precursor **6.1** in enantiomeric excess.

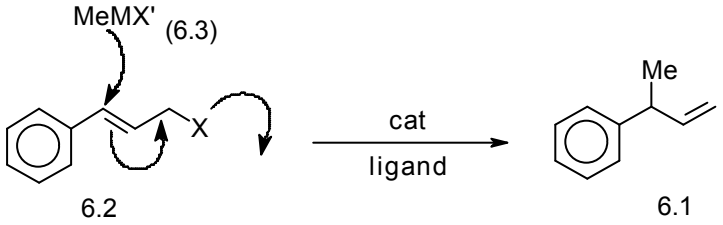
We saw an appropriate alternative reaction for the preparation of **6.1** in the nucleophilic substitution of an allylic species by a methylmetallic reagent in a S_N2' fashion (Scheme 6.1, Eq. 2). In the following section, mechanisms together with theoretical and practical findings will be discussed. In Section 6.3, the strategy towards enantioselective S_N2' reactions is discussed, based on some inspiring reports. S_N2' reactions in practical sense are discussed in Section 6.4, followed by an epilogue (Section 6.5) and conclusions in Section 6.6.

6.2 An alternative route to compound 6.1: the S_N2' reaction

It is evident that from methylmetallic species **6.3** and cinnamyl compounds **6.2**, the profen precursor **6.1** can be prepared by the γ–selective S_N2' reaction. The methyl group then must attack at the benzylic position of the allylic cinnamyl compound and, concomitant with movement of the double bond, the leaving group X eliminates under formation of **6.1** (Scheme 6.2). On closer examination, the carbon-carbon bond formation in S_N2' fashion also can be considered as a cross coupling reaction. In order to avoid confusion, we will refer to the present reaction as a *S_N2' reaction* or *γ-selective (substitution) reaction*. The S_N2' reaction is an essentially different approach to **6.1**, compared with the cross coupling reaction described in the Chapters 2, 4, and 5. Instead of the vinyl group, the methyl group is coupled to the benzylic position. When we compare both reactions with regard to stereochemistry, the asymmetric cross coupling reaction is a

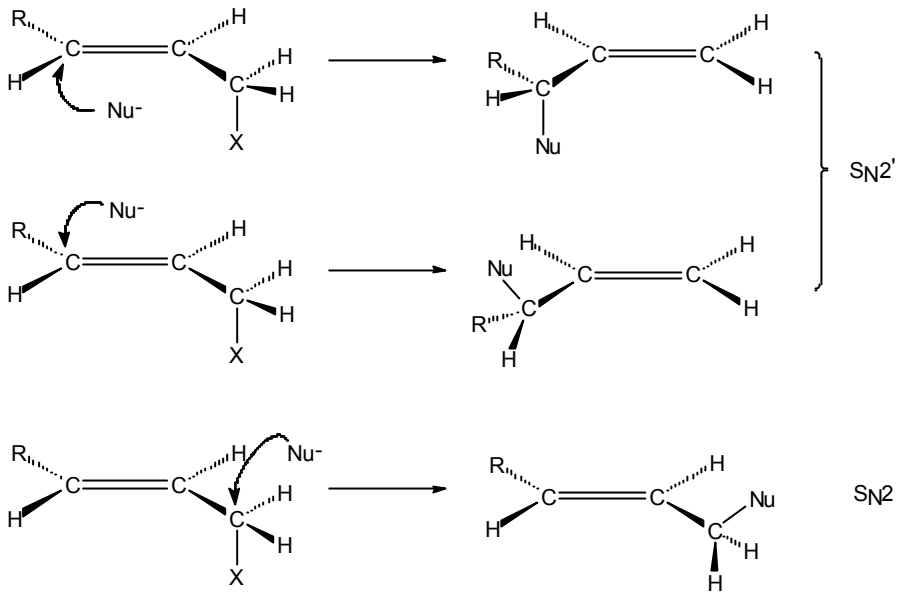
dynamic kinetic resolution of a racemic 1-phenylethyl metallic species, and **6.1** can be obtained in high optical yield. On the other hand, the S_N2' reaction involves the attachment of a methyl group to an allylic, prochiral[a] position by a nucleophilic substitution.

Three pathways are possible for nucleophilic substitution of allylic substrates. The nucleophile may attack the π-bond at the γ-position in either a (1) syn or (2) anti fashion relative to the leaving group, the S_N2' mechanism, or (3) may substitute at the saturated α-position by an S_N2 mechanism. The S_N2' reaction is a bimolecular nucleophilic displacement of a nucleofuge by a nucleophile, accompanied by an allylic rearrangement. The regiochemistry (α- *versus* γ-attack) has been an important problem of this reaction, and often mixtures of S_N2' and S_N2 products are obtained.[1] In addition to the stereochemistry of the reaction, the question remains whether the S_N2' displacement proceeds in a stepwise manner through a stable intermediate or in a concerted fashion. This topic has been a subject of controversy.[2,3]



Scheme 6.2

[a]Prochiral is the term used for an achiral compound which can be converted into a chiral compound after one chemical step.

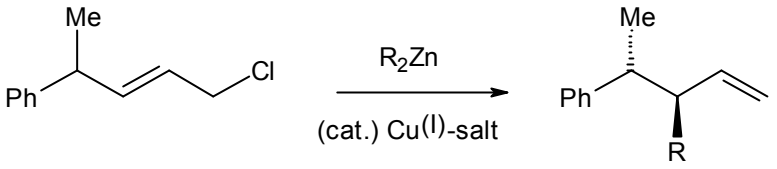


Scheme 6.3

Recent theoretical studies on the identity of S_N2' reactions propose that the gas phase degenerate nucleophilic reactions of an allylic system with nucleophiles X^- = H^-, F^-, Cl^- (which in these studies are leaving groups simultaneously) proceed by different mechanisms depending on X (Scheme 6.3). The stepwise pathway, with the rate-limiting breakdown of the intermediate, is favoured for nucleophile (and leaving group) X = H, which has a relatively low electronegativity. For the highly electronegative X = Cl, the direct S_N2 displacement mechanism is favoured. In the case of X = F, the intermediate of the syn form is less stable and all three mechanisms (*vide supra*) can compete. In this case the rotational barrier of the CH_2F group prevents the anti-S_N2' path from going through the syn-S_N2' intermediate, as found for X = H. The anti-S_N2' reaction provides the lowest energy path, which is found to proceed concertedly.[3]

In a practical sense, standard Gilman reagents (R_2CuLi) have been successfully applied in S_N2' reactions, though their γ-regioselectivity is unreliable. The scope has been extended

to reagents based on combinations[b] of copper(I) and Lewis acidic metals as Mg-Cu,[4] Zn-Cu[5,10] and Ti-Cu.[5,6] These combinations have been found to give consistently high γ-regioselectivity. Stereoselective S_N2' reactions have been extensively reported on the prochiral position of chiral, racemic substrates, affording diastereomers as depicted in Scheme 6.4. [6,7,8,13]



Scheme 6.4

At the time of these investigations, asymmetric catalysed enantioselective S_N2' reactions on achiral allylic species had no precedent, to our knowledge.

6.3 Strategy towards asymmetric catalysed S_N2' reactions

Introduction

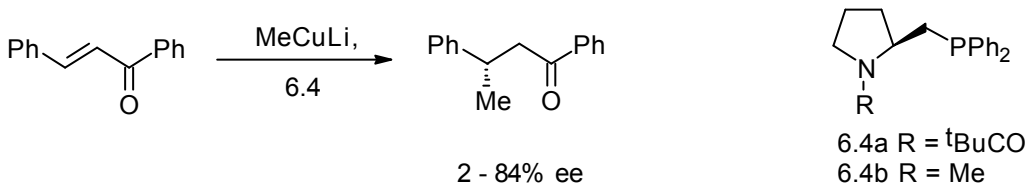
We expected that an S_N2' reaction in an asymmetric catalysed version has the potential to serve our purposes very well, affording **6.1** in enantiomeric excess. The combination of ligand, catalyst and methyl-metal compound has to meet the following conditions: First, the S_N2' substitution must take place highly γ-selectively, without competing formation of the S_N2 product. Second, in the absence of catalyst, no reaction must occur. In this way, the blank reaction without chiral induction is prevented. Third, the methyl transfer in the S_N2' substitution must occur in an enantioselective manner.

The scope of S_N2' reactions is broad,[8] even for the synthesis of a closely defined compound as **6.1**. The outlines we have drawn were inspired by reports from the literature (*vide infra)*. For a better understanding of the selection we made of catalysts and ligands, we will review some papers concerning copper chemistry and S_N2' chemistry. One of the papers deals with enantioselective conjugate addition reactions with organocopper species, the others relate to S_N2' chemistry.

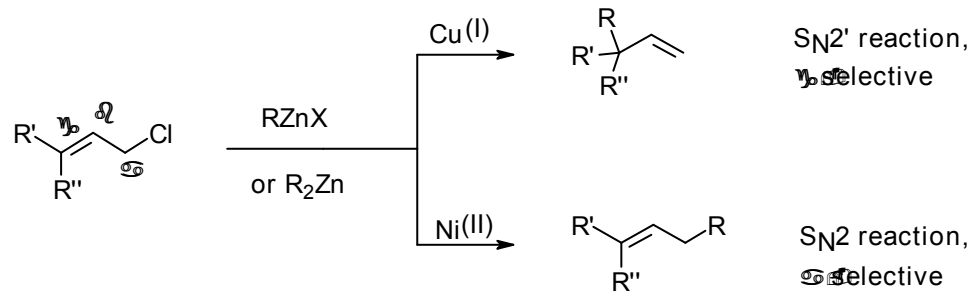
[b] In stoichiometric and, more recently, in catalytic amounts.

Recent developments

In the area of organocopper chemistry, enantioselective conjugate addition is a rapidly developing area. Chiral modification of heterocuprates has been the prototype of these approaches, wherein chiral amides, alkoxides and thiolates are employed as chiral components of the cuprates.[9] In this section we focus on another, scarcely used, approach where chiral external ligands have been used as asymmetric controllers. In 1992, Tomioka *et al*. derived some ligands from proline.[9] In enantioselective conjugate additions of lithium dimethylcuprate to chalcone in the presence of these ligands (Scheme 6.5), remarkable differences in stereoselective behaviour were observed. Conjugate Me_2CuLi additions in the presence of aminophosphine **6.4b** gave only 2% *ee*, whereas amidophosphine **6.4a** afforded 84% *ee*. This effect is attributed to a selective metal differentiating coordination of the carbonyl oxygen to the lithium atom, and of the phosphorus to the copper atom.



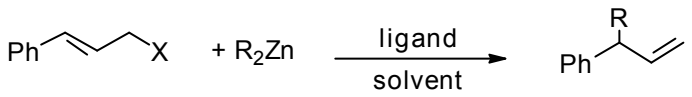
Scheme 6.5



Scheme 6.6

In 1988, Nakamura *et al*. showed that organozinc species undergo highly S_N2'-regioselective $Cu^{(I)}$ catalysed allylation reactions.[10] They found that the mode of regioselection shifted

from S_N2' (γ) to S_N2 (α), simply by switching from $Cu^{(I)}$-based to $Ni^{(II)}$-based catalysts (Scheme 6.6). γ–Regioselectivity (S_N2' reaction) of 98% was obtained with $CuBr{\bullet}SMe_2$ as catalyst. In contrast to copper reagents based on RLi or RMgX, the [RZnX – $Cu^{(I)}$-catalyst] reagent shows high chemoselectivity and neither reacts with allylic acetates nor with alkyl halides. In 1993, Nakamura *et al*. reported that a regio- and stereoselective allylation of organozinc reagents was not completely limited to Cu-based reactions.[11] Dialkylzinc reagents could undergo highly regio- (Scheme 6.7) and diastereoselective (Scheme 6.8) S_N2' allylation reactions in the presence of coordinating additives such as HMPA, TMEDA, or DMF. A monodentate amine, Et_3N, proved to be ineffective. Regio- and diastereoselectivity as well as reaction rate depended on the nature of the solvent. For instance, the reaction in pure hexane in comparison with THF is much less selective (50% *versus* 97%) and much slower (9% *versus* 87% yield).

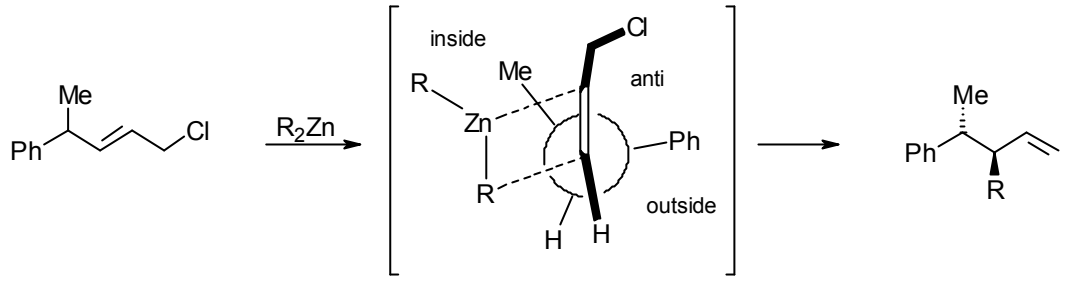


X = Cl, Br, $OP(O)(OEt)_2$; ligand: DMF, HMPA, TMEDA; solvent: THF, hexane

Scheme 6.7

For the allylation of organocopper reagents, two mechanisms have been proposed. (1) The copper mediated reactions are presumed to proceed through a $Cu^{(III)}$-allyl intermediate, on attack of the copper atom to the olefinic carbon. The mechanism through $Cu^{(III)}$, however, cannot be applied to the organozinc mediated reactions, since such a hypervalent zinc species is improbable. Another proposed mechanism involves a nucleophilic attack of the alkyl group on the copper atom, leading directly to the allylation product. (2) Nakamura *et al.* observed that for organocopper and organozinc reagents the sense and level of the diastereoselectivity were surprisingly similar.[12] It is probable that the second mechanism is also applicable to the organocopper reactions. The observed stereoselectivity conforms to Cram's rule proposed for carbonyl additions. Though the mechanisms of the

present allylation reaction and the carbonyl addition may seem different from each other, similarity may become rational if the allylation reaction is viewed as a carbometalation-like reaction (Scheme 6.8).[11]



Scheme 6.8

From the above reports we conclude that a highly γ–selective allylation reaction of the organometallic species depends on appropriate choice of the organometallic compound or intermediate, the allylic reagent and the solvent. In our search to obtain catalytic enantioselective S_N2' reactions we were interested in the following: *i*) which reagents provide high γ-regioselectivity in S_N2' substitution reactions, and: *ii*) which asymmetric catalyst would potentially induce enantioselectivity, as well as high γ-regioselectivity.

i) Reagents and regioselectivity

We have seen in the above reports that the organometallic reagent in S_N2' reactions is not only limited to organocuprates. Organozinc reagents in the presence of a copper catalyst can be applied successfully in γ-selective allylation reactions. Also, on addition of appropriate coordinating additives to the organozinc species, even the Cu-based catalyst can be omitted. Among the reagents that have been applied successfully in the alkyl transfer were organometallic compounds or intermediates based on Mg, Li, Zn, and Ti. Levisalles *et al*. reported that the regioselectivity in substitution reactions on terpene acetates, reversed from α to γ on changing $CH_3(X)CuLi$ from X = CH_3 to X = CN. With organocuprate X = SPh, mixed behaviour was observed.[13] The possibility of two geometric isomers around Cu in the

$CH_3(CN)CuLi$ π-allyl intermediate is given as explanation for this behaviour. In the case of $(CH_3)_2CuLi$, it seems reasonable that the proposed π-allyl copper complex retains stereochemistry and is sterically disposed to transfer the CH_3 group to the less hindered carbon. So far, adequate rationalization has not been given for the behaviour in all experiments.[8]

For the allylic reagent, an appropriate leaving group is required in order to realize **6.1**. This condition is easily fulfilled since, for instance, cinnamyl acetates and halides (Scheme 6.1, Eq. 2, **6.2a-c**) are commercially available, and are easy to handle. Significant effects of the leaving group on regioselectivity have been found.[14] Which type of leaving group is to be chosen depends on the choice of organometallic compound or catalytic intermediate. In Cu-catalysed reactions with organozinc reagents, we expected **6.2a-c** (Scheme 6.1, Eq. 2) to be proper reaction partners. Further, it is probable that the enantioefficacy in the reaction is solvent dependent, like the asymmetric cross coupling reactions described in Chapter 2, 4 and 5.

ii) Asymmetric ligands in S_N2' reactions

We speculated that appropriate asymmetric ligands for the organometallic intermediate might induce chirality at the γ-position. In organocuprate or $Cu^{(I)}$-catalysed reactions, asymmetric ligands may chelate to the Cu centre, and/or to the organometallic species. In S_N2' allylation reactions with organozinc reagents, asymmetric ligands may perform the function of polar additives. We expected that these asymmetric complexes may approach the allylic moiety in a syn- or anti-selective fashion and transfer the methyl group in this way. Chelation of an asymmetric organometallic intermediate to the leaving group, prior to alkyl transfer, may also play a role in the enantioselectivity.

The above reports inspired us in the design of an appropriate ligand. In both the conjugate addition of organocuprates[9] (Scheme 6.5), and the γ-selective allylation of organozinc species[11] (Scheme 6.6), superior ligands contain nitrogen, phosphorus and oxygen. Further, a sulphur based ligand, dimethylsulphide, was used by Nakamura to stabilize

the $Cu^{(I)}$-catalyst in Scheme 6.6.[10] We considered that α-amino acid derived ligands that contain nitrogen, phosphorus or sulphur, as described in Chapter 3, may serve very well the purpose of asymmetric ligands for catalysts in regio- and enantioselective S_N2' reactions. In our group, and in the present research, homologues of methphos have been developed. These tridentate ligands are interesting ligands for this reaction. Another interesting ligand is the proline-derived amidophosphine **6.4a** (see Scheme 6.5), which is an effective ligand in the conjugate addition reaction. We expected that **6.4a** may give a proper chelation to a **6.2a** - methyl cuprate complex, when applied in the S_N2' reaction. This will be discussed under the heading *Organozinc reagents in S_N2' reactions*, in Section 6.4.

6.4 Substitution reactions in S_N2' fashion
Organozinc reagents in S_N2' reactions

The choice of methylzinc compounds as alkylating reagents gave us the opportunity to select two types of catalysed S_N2' reactions, namely, on the one hand [MeZnX - $Cu^{(I)}$] couples and on the other hand [RZnX - polar additive] combinations. In either case, asymmetric ligands can be applied as a ligand for $Cu^{(I)}$ or as a coordinating additive for RZnX.[15] Methylzinc halide (MeZnX•LiX, X = Cl, I) was prepared by a metathesis reaction of MeLi•LiX (X = I or Cl) with $ZnCl_2$ in THF.[c] The method used for the preparation of the organozinc reagent seems to play no pivotal role in regioselectivity. Organozinc reagents prepared by a metathesis reaction,[10,11] as well as through a direct reaction between zinc and organic halides,[16] provide highly S_N2'-selective organozinc reagents. The commercially available 2.0 M Me_2Zn solution in toluene proved less practical in the present investigation. We found that product **6.1** and the solvent, toluene, are difficult to separate by distillation, probably due to the formation of an azeotrope.

[c] Later on, we made use of MeLi•LiCl in EtO, kindly provided by R. Duchateau.

Asymmetric catalysts for S_N2' reactions with methylzinc reagents

We performed some pilot experiments with $Cu^{(I)}$-catalysed S_N2' reactions (Scheme 6.1, Eq. 2) using achiral ligands like dimethyl sulphide and 2,2'-bipyridine (entries 1 and 2). The MeZnX solution, in the presence of 5-10 mol% of [$Cu^{(I)}$ - ligand] combination, was treated with the cinnamyl compound. The chemical yields of the substitution product obtained with dimethyl sulphide and 2,2'-bipyridine were moderate: 40% and 30% respectively, but in fair S_N2' : S_N2 regioselectivity of 80 : 20 and 67 : 33, respectively (^{1}H NMR). Further, we employed asymmetric ligands derived from amino acids[d] in the above described S_N2' reaction. These experiments were inspired by literature analogues, based on considerable empirical research. With **3.11** (Section 3.3) as ligand (entry 3), the reaction proceeded with a moderate S_N2' : S_N2 regioselectivity (60 : 40, ^{1}H NMR), and **6.1** was obtained in 42% chemical yield. However, no chiral induction took place (no rotation observed). With tridentate compound **3.24**, (Section 3.4) containing phosphorus, nitrogen and sulphur as heteroatoms, **6.1** was obtained in low yield (13%) as a racemate (chiral GC column).

Table 6.1 S_N2' reactions on **6.2** with [Zn - CH_3] species (cf. Scheme 6.1, Eq. 2)

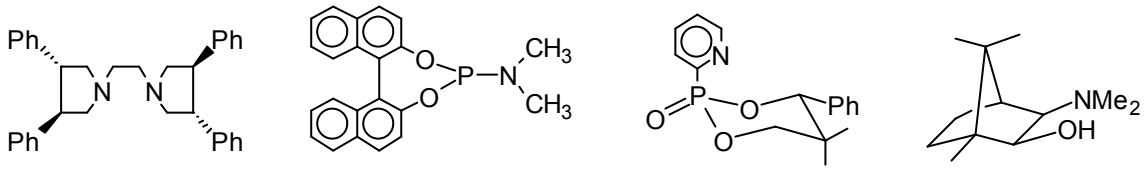
entry	ligand	$Cu^{(I)}$-salt	regioselectivity (γ : α)	% yield (γ)
1	Me_2S	CuBr	80 : 20	40
2	bipy[a)]	CuBr	67 : 33	30
3	**3.11**	CuBr	60 : 40	42
4	**3.24**	CuBr	n.d.[b)]	13
5	**6.5**	CuBr	n.d.[b)]	90
6	**6.6**	CuBr	n.d.[b)]	70
7	**6.7**	---	n.d.[b)]	30
8	**6.8**	CuBr	70 : 30	25

a) 2,2'-bipyridine b) n.d.: not determined

The next asymmetric ligands were selected on basis of their similarity to achiral analogues, as reported by Nakamura *et al.* (*vide supra*).[11] These ligands were kindly provided by

[d] See Chapter 3.

colleagues from the Chemistry Department (Figure 6.1).[e] In these empirical studies we determined the enantioselectivity due to the asymmetric ligand and not the regioselectivity. The chemical yields of **6.1** in these experiments were comparable to the experiments with achiral catalysts, being about 40%. We considered **6.5** as an asymmetric analogue of TMEDA. In entry 5, **6.1** was obtained in 90% chemical yield as a racemate. Further, we have used bis-β-naphthol derived compound **6.6**. This ligand furnished **6.1** in 70% yield, but without enantiomeric excess.[f] We fancied that with compound **6.7**, the P=O and the aromatic nitrogen in the pyridine appendage would give an appropriate chelation to the zinc reagent, like e.g. HMPA in [RZn-polar additive]-type S_N2' reactions.[g] Under reaction conditions similar those reported by Nakamura,[11] **6.1** was obtained in 30% chemical yield as a racemate.



6.5 6.6 6.7 6.8

Figure 6.1

Besides the S_N2' reactions with the above ligands, we performed several studies with **6.8**. In these studies, we used 5 mol% $Cu^{(I)}Br$ as catalyst.[10] We rationalized[h] that 10 mol% of **6.8** would chelate for a part to the copper catalyst and for another part to the methylzinc species. When we allowed the methylzinc reagent to react with **6.2b**, a dark brown, complex reaction mixture was obtained. Working under the assumption that this coloration was due to halide formation,[i] we then

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[e]Ton (T.R.) Vries, Ron (A.J.R.L.) Hulst, Bas (A.C) Dros and André (A.H.M) de Vries are thanked for the generous gift of compounds to be ligands in this reactions. These compounds are 6.5, 6.6, 6.7, and 6.8, respectively.

[f] This result was later supported by results of A.H.M. de Vries, using a similar ligand, where nitrogen was substituted by two isopropyl groups instead of two methyl groups. (A.H.M. de Vries, PhD thesis 1996).

[g]cf. ref. 11.

[h]Analogous to additions of dialkylzinc to RR'C=O bonds.

[i] From triiodide, bromine or another brown-coloured halide combination.

chose **6.2c** as allylic substrate. This combination provided also a brown coloured crude reaction mixture, containing **6.1** (NMR). Purification of this crude material by routine distillation furnished a dark brown, complex reaction mixture, similar to what we observed in the previous experiment. The coloration may be due to the presence of iodide salts in the reaction mixture, resulting from MeZnX•LiX, X = Cl, I. We expected no colouring of the reaction mixture with commercially available Me_2Zn solution in toluene, since this solution does not contain halides. The resulting reaction mixture was coloured brown after work up and turned rapidly into a darker coloured liquid on standing. In a following experiment, $Cu^{(I)}Br$ was omitted in order to trace the source of brown coloration. The S_N2' reaction was presumed to occur *via* an [MeZn, **6.8**] combination. No colouring occurred, but still a complex reaction mixture was obtained. We identified the formation of a small amount of **6.1** by GC and NMR (<5%). In a $Cu^{(I)}Br$ catalysed experiment with as ligand the alkoxide of **6.8**, entry 8, the brown coloured crude material was obtained with an S_N2' : S_N2 ratio of 70 : 30. The S_N2' product could be isolated in 25%. Attempts to prevent the continuing return of the brown colour failed.[j] Since the coloration of the reaction mixture probably stems from the $Cu^{(I)}Br$ catalyst, we changed to $Cu^{(I)}CN$ as catalyst.

Methylzinc reagents in S_N2' reactions: conclusions

From the above results, we concluded that the S_N2' reactions performed with methylzinc species are moderately γ-selective. In cases where asymmetric ligands have been applied, no chiral induction was observed. Moreover, we observed that S_N2' reactions may take place without a catalyst.[k] In the present research, however, the intermediacy

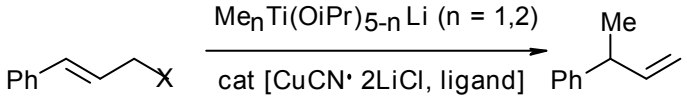
[j] The brown colour vanished periodically on washing the crude material extensively with sodium metabisulphite (4 times) and triethyl phosphite (1 time). The product, purified by distillation, was still slightly contaminated, according to the pale pink colour.

[k] We emphasize that the ensuing result was not investigated into detail, for which reason an extensive discussion is omitted. We know from the literature that saturated alkylzinc species do not react with alkenes or aldehydes. Addition of a ligand or auxiliary to the organozinc species distorts the linear geometry of the zinc-alkyl bond and accelerates the alkyl transfer reaction (ref. 15). Therefore, it is peculiar that we detected a trace of 6.1 in a qualitative experiment where Me_2Zn and 6.2c have been stirred without any additives as (polar) ligands or catalysts. Since the GC signal of 6.1 was superimposed upon the very broad tail of the toluene signal, the yield could not be determined;

of an asymmetric catalyst is a prerequisite for the intended chiral induction. On that account, we shifted our strategy and performed for this study some closing experiments with organotitanium reagents.

Organotitanium reagents in S_N2' reactions

We have selected organotitanium reagents as an alternative for methylzinc reagents in S_N2' reactions. $Cu^{(I)}$-catalysed S_N2' reactions with organotitanium reagents have been found to give high regioselectivity.[6] Analogously to successful γ-selective substitution reactions with *n*-butyltitanate complexes,[6b] we employed methyl-titanate complexes in the S_N2' reaction (Scheme 6.9). These ate-complexes, $[MeTi(OiPr)_4Li]$ and $[Me_2Ti(OiPr)_3Cl]$, are easily prepared from MeLi and $Ti(OiPr)_4$ or 2 MeLi and $ClTi(OiPr)_3$, respectively. Generally, 8 mol% of the ligand was stirred with CuCN•2LiCl at 0°C, prior to addition to the titanate complex (1.5 eq.). To the resulting mixture 1.0 equivalent of cinnamyl compound was added at -70°C. The mixture was stirred overnight, during which time it was allowed to warm to ambient temperature. After careful hydrolysis of the reaction mixture with moist hexane and subsequent distillation, the material was subjected to chiral GC analysis.



Scheme 6.9

With these [MeTi-Cu] combinations, the chemical yield and regioselectivity of **6.1** improved significantly, in comparison with the [MeZn-catalyst] combinations (*vide supra*). On the average, we obtained **6.1** in 70% yield using this method. In all cases, we did not observe the formation of S_N2 product (GC). We established that this reaction is highly Cu-catalyst

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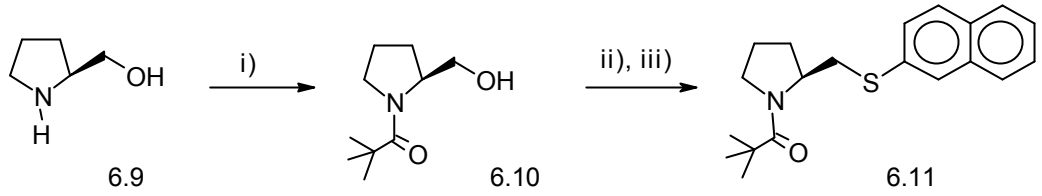
toluene and 6.1 are inadequately separated by distillation (see Section 6.4 Organozinc reagents in S_N2' reactions). We assume that the reaction may have taken place for a few percent without a ligand as accelerator, or that another mechanism is involved. It must be noted that we were not able to reproduce this experiment.

dependent. In a standard experiment where we treated **6.2a** with [$Me_2Ti(OiPr)_3Li$], no trace of **6.1** was detected in the case when the $Cu^{(I)}$-catalyst was omitted nor was formation of α-regioselective product observed. Since we have found that organozinc reagents perform S_N2' reactions without catalyst, *vide supra*, the Ti-Cu combination is promising for our purpose.



6.9 6.10 6.11

i) pivaloyl chloride; ii) methanesulphonyl chloride; iii) 2-naphthalenethiol.

Scheme 6.10

Synthesis of compound 6.11

One of our aims in the enantioselective S_N2' reaction (Scheme 6.1, Eq. 2) was to employ **6.4a**, since this compound has proven to be a successful ligand in enantioselective conjugate additions (*vide supra*).[9] For the method of preparation of **6.4a**, Tomioka *et al.* refer to a Japanese patent,[17] (abridged in Chemical Abstracts)[18], and to a report of Kagan *et al.*[19] The latter report describes a general procedure to convert alcohols into phosphines. Several attempts, however, to obtain **6.4a** from **6.9** by the above mentioned and other approaches were unsuccessful.[20] Whatever the explanation, this result prompted us to modify our strategy with regard to the ligand. We expected that an amidosulphide ligand (eg. **6.11**, Scheme 6.10) would be an appropriate substitute for the intended amidophosphine. In order to mimic partly the two aromatic moieties that are present in the diphenylphosphino group, we chose a 2-naphthyl group. Compound **6.9** was allowed to react with pivaloyl chloride, affording **6.10** in 96% yield. Analogously to the synthesis of aminosulphides described in Chapter 3, compound **6.10** was converted into the corresponding mesylate which reacted *in situ* with a mixture of KO^tBu and 2-naphthalenethiol in THF to give **6.11** in 53% yield.

Asymmetric catalysts for S_N2' reactions with methyltitanate reagents

In the S_N2' reaction (Scheme 6.9) we used **6.11** as ligand for the copper catalyst. Further, we selected **3.9b**. (see Section 3.2), which is an 'on shelf' ligand. The chemical yields of **6.1** in the S_N2' reactions catalysed by **6.11** and **3.9b** were comparable: 71% and 69%, respectively (Table 6.2, entries 1 and 2). These are fair yields, compared with experimental results of Nakamura, where a butyl group is introduced on the same allylic substrate. The chemical yields are at least higher than the yield obtained by Nakamura with the $CuBr{\bullet}SMe_2$ catalyst (57%). On basis of the above results, it is tempting to suggest that **6.11** and **3.9b** are better as ligands in this reaction than dimethylsulphide. Yet, this is not experimentally demonstrated by a $CuBr{\bullet}SMe_2$ catalysed $_NS2'$ reaction between methyl-titanate and **6.2a**. At least, we can conclude that **6.11** and **3.9b** are moderately successful ligands. In the S_N2' reaction with **3.9b** as ligand, the yield may be improved by using **6.2a** instead of **6.2c**. The regioselectivity of both experiments is, from GC measurements, absolutely γ-selective, in agreement with literature data (>99%).[6b] No trace of α-product, phenyl-1-butene, was detected by GC. To our disappointment, both experiments afforded **6.1** in racemic form on the basis of a chiral GC analysis.

Table 6.2 *S_N2' reactions on **6.2** with [Ti - CH_3] species (cf. Scheme 6.9).*

entry	ligand	regioselectivity (γ : α)	% yield (γ)
1	**6.11**	>99 : <1	71
2	**3.9b**	>99 : <1	69

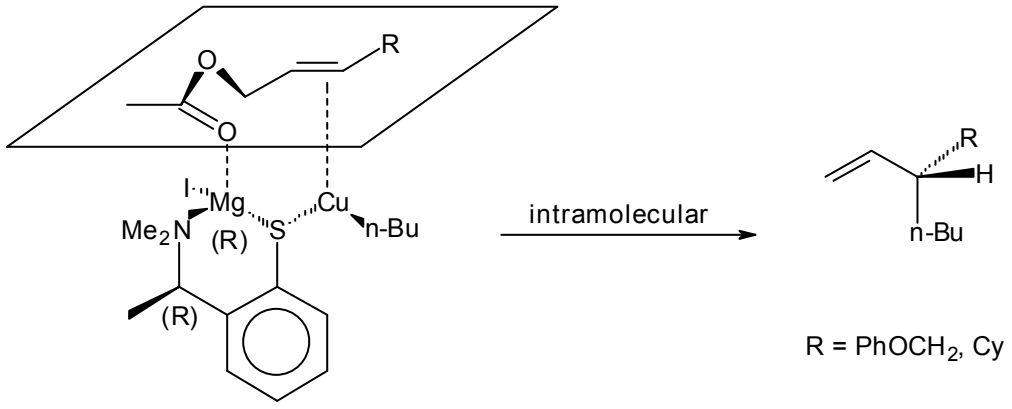
$CuCN{\bullet}2LiCl$ was used as catalyst.

Methyltitanate reagents in S_N2' reactions: conclusions

From the above results, we concluded that the S_N2' reactions performed with methyltitanate species are highly γ-selective. In cases where asymmetric ligands have been applied, no chiral induction was observed.

6.5 Epilogue

Recently, Van Koten *et al*. reported asymmetric catalysed enantioselective S_N2' reactions on two achiral allylic substrates, **6.12a** and **6.12b**.[21] Asymmetric arenethiolatocopper(I) complexes (Scheme 6.11) afforded an enantioselectivity of up to 42% between those allylic acetates and *n*–butylmagnesium halide. The rationale for the model proposed for enantioselectivity is interesting. The authors postulate the acetate and the alkene group of the allylic moiety to anchor to the magnesium and the copper moiety, respectively, of the catalytic intermediate. The enantioselectivity in the alkyl transfer was explained on the basis of coordination of the copper-alkyl group to the alkene moiety, in combination with the configuration of the (chiral) magnesium centre. They used an equilibrium between two possibilities derived from molecular modelling to explain the moderate *ee* of only 42% (underscoring the subtleness of this enantioselection). Although it is stated that there is little steric interaction between the allylic substrate and the alkyl group containing catalytic intermediate, the question remains what will happen to the moderate enantioselectivity if the *n*-butyl group is replaced by a smaller group like methyl. In other words: can a profen precursor like 3-phenyl-1-butene be realized by this method? An explanation for the non-enantioselectivity in the S_N2' reaction that we have performed with methylmetallic reagents, may be that the methyl group is too small compared to, for instance, the *n*-butyl group.



Scheme 6.11

Also, we have to bear in mind that the enantioselectivity in the above report is explained on basis of a mechanism that is applicable to organocuprates, namely *via* a $Cu^{(III)}$ intermediate, but not to organozinc species (cf. Section 6.3 - *Recent developments*). This emphasizes that possibly two or more mechanisms exist for the S_N2' reaction between organometallic reagents and allylic substrates.

6.6 Conclusions

In this chapter, the application of asymmetric ligands in catalysed S_N2' reactions of methylmetallics on allylic cinnamyl species towards enantiomeric enriched **6.1** is described. Attempts to make the methyl transfer enantioselective by addition of various asymmetric ligands to the [MeZn, $Cu^{(I)}$-catalyst] couple, failed. Also S_N2' reactions with [MeZn, chiral, polar additive] as methyl donating complex failed, regarding to enantioselectivity. The γ-selectivity of S_N2' reactions with [MeZn, chiral, polar additive] reagents was moderate (up to 70%). Methylzinc reagents in S_N2' reactions on cinnamyl species were not found to be absolutely catalyst dependent.

S_N2' reactions on cinnamyl species with [Me-titanate, $Cu^{(I)}$-catalyst] combinations furnished **6.1** in 70% yield, on the average. Attempts to make the methyl transfer enantioselective, on addition of asymmetric ligands to the [Me-titanate, $Cu^{(I)}$-catalyst] couple, failed. Substitution reactions on cinnamyl compounds with methyltitanates were highly γ-selective (> 99%).

Recent developments in enantioselective S_N2' reactions with organocuprates (Section 6.6) show that this is a promising area for asymmetric catalysis. The *ee*'s that have been reported are moderate (up to 45%), and the proposed intermediate responsible for enantioselection is based on cuprate chemistry, *via* $Cu^{(III)}$ intermediates. Since an alternative mechanism has been proposed for organozinc species,[11,12] which is also applicable to organocuprates, the mechanism of enantioselection becomes more unclear: a promising new area for further research.

6.7 Experimental section

General remarks: see Sections 3.6 and 4.9.

Synthesis of MeZnX•LiX (typical procedure)

To $ZnCl_2$ (2.73 g, 20.0 mmol) in THF (20 mL) was added by syringe MeLi•LiX (1.2 M, 17 mL, 20 mmol). The resulting solution of MeZnX•LiX is further denoted as MeZnX, where X = halide, dependent on the methyl halide used to prepare MeLi, and on zinc halide, being $ZnCl_2$ in the present investigations.

S_N2' reactions with methylzinc reagents on cinnamyl compounds (6.2)

[*ligand - catalyst combination*]:

[*Me_2S - CuBr*] *and standard work up*: To a mixture of [$CuBr•SMe_2$] (0.50 g, 2.43 mmol) in THF (5 mL) was added MeZnX (1.2 M, 17 mL, 20 mmol) at 0°C. The mixture was stirred for 15 min, after which **6.2b** (4.04 g, 20 mmol) in THF (5 mL) was added at 0°C. The reaction mixture was stirred for 18 h at ambient temperature. The mixture was poured in a saturated NH_4Cl solution (100 mL) extracted with Et_2O (2 x 50 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), concentrated under reduced pressure and distilled under standard conditions (cf. Chapter 4) to give **6.1** (56%).

[*2,2'-bipyridine - CuBr*]: The same procedure was followed as for [Me_2S - CuBr] as catalyst; **6.1** was obtained in 30% yield.

[L-*2-Dimethylamino-1-(2-naphthylthio)-3-phenylpropane (3.11) - CuBr*]*:* To a mixture of **3.11** (80 mg, 0.25 mmol) and CuBr (36 mg, 0.25 mmol) in Et_2O (5 mL) was added MeZnX (1.0 M in Et_2O, 5 mL). A solution of **6.2b** (985 mg, 5 mmol) in Et_2O (5 mL) was added dropwise at –40°C. After usual work up procedure, 465 mg of crude material was obtained, a mixture of S_N2' and S_N2 products in a ratio of 60 : 40, where **6.1** was obtained in 42% yield.

[D-*2-Dimethylamino-1-diphenylphosphino-5-(2-propylthio)-pentane (3.24) - CuCN*]: A previously prepared mixture of MeLi•LiCl (1.0 M in Et_2O, 10 mL, 10 mmol) and $ZnCl_2$ (1.126 g, 5 mmol), was added to a mixture of **3.24** (78 mg, 0.20 mmol), CuCN (22 mg, 0.25 mmol) and **6.2a** (0.84 mL, 5 mmol) in Et_2O (12

mL) and the reaction mixture was stirred for 18 h at ambient temperature. The standard work up procedure led to **6.1** (13%) as a racemate (GC, Lipodex C).

[*(All-R)-N,N-ethylene-bis-(3,4-diphenylpyrrolidine (6.5) - CuBr*]: To a mixture of **6.5** (354 mg, 0.75 mmol), and CuBr (100 mg, 0.70 mmol) in Et_2O (2 mL) was added MeZnX (1.0 M in Et_2O, 15 mL, 15 mmol) at –40°C. A solution of **6.2b** (2.96 g, 15 mmol) in Et_2O (20 mL) was added at –40°C, and the reaction mixture was stirred for 18 h at ambient temperature. The standard work up procedure led to **6.1** (90%) as a racemate (GC, Lipodex C).

[*O,O'-(1,1'-Dinaphthyl-2,2'-diyl)-N,N-dimethylphosphorus amidite (6.6) - CuCN*]: To a mixture of **6.6** (89 mg, 0.25 mmol), CuCN (22 mg, 0.25 mmol) and a solution of **6.2c** (763 mg, 5 mmol) in THF (20 mL) was added Me_2Zn (2.0 M in toluene, 3.75 mL, 7.5 mmol), at –60°C. The reaction mixture was stirred for 18 h at ambient temperature. The standard work up procedure led to **6.1** (ca. 70%) as a racemate (GC, Lipodex C).

[*(S)-2-(2-Pyridinyl)-2-oxo-4-(S)-phenyl-5,5-dimethyl-1,3,2-dioxaphosphorinane (6.7) - Me_2Zn*]: To a solution of **6.7** (303 mg, 1.0 mmol) was added Me_2Zn (2.0 M in toluene, 0.25 mL, 0.50 mmol) at –70°C, followed by **6.2c** (0.055 mL, 0.3 mmol). The reaction mixture was stirred for 18 h. The standard work up procedure led to **6.1** (ca. 30%) as a racemate (GC, Lipodex C).

[*(–)-Cis-exo-N,N-dimethyl-3-aminoisoborneol ((–)-DAIB), (6.8) - CuBr*]:

S_N2' on 6.2b: To a solution of **6.8** (296 mg, 1.5 mmol) and CuBr (108 mg, 0.75 mmol) in Et_2O (5 mL) was added MeZnX (1.0 M in Et_2O, 15 mL, 15 mmol). **6.2b** (2.95 g, 15 mmol) was added at 0°C, and the reaction mixture was stirred for 18 h at ambient temperature. The standard work up procedure led to a dark brown oil, that turned out to be a complex reaction mixture (^{1}H NMR). Optical rotation was not determined.

S_N2' on 6.2c: This experiment was repeated on a 10 mmol scale with **6.2c**. A similar brown coloured complex residue was obtained, and no optical rotation was determined.

S_N2' on 6.2b by Me_2Zn: To a solution of **6.8** (197 mg, 1.0 mmol)

and CuBr (72 mg, 0.50 mmol) in toluene (20 mL) was added Me_2Zn (2.0 M in toluene, 5,0 mL, 10 mmol). At 0°C **6.2c** (1.52 g, 10 mmol) in toluene (5 mL) was added. The reaction mixture was stirred for 18 h at ambient temperature. The standard work up procedure led to a dark brown oil that turned out to be a complex reaction mixture (^{1}H NMR). Optical rotation was not determined.

S_N2' on 6.2b without $Cu^{(I)}$-salt: To a solution of **6.8** (99 mg, 0.50 mmol) in toluene (5 mL) was added Me_2Zn (2.0 M in toluene, 6.0 mL, 12 mmol). The solution was stirred for 20 min. and cooled to –78°C and **6.2c** (1.53 g, 10 mmol) in toluene (5 mL) was added. The reaction mixture was stirred for 18 h at ambient temperature. The standard work up procedure led to crude material in which **6.1** among other compounds could be detected (GC). **6.1** could not be isolated from toluene. Optical rotation was not determined.

S_N2' on 6.2b with (6.8-alkoxide): To a solution of **6.8** (197 mg, 1.0 mmol) in THF (2 mL) was added *n*-BuLi (1.6 M in hexane, 0.625 mL, 1.0 mmol) followed by CuBr (72 mg, 0.5 mmol). To the resulting mixture was added MeZnX (1.0 M in Et_2O, 10 mL, 10 mmol) and **6.2c** (1.53 g, 10 mmol) in Et_2O (5 mL). To remove the repetitive return of the brown coloration, the brown residue was washed twice with $Na_2S_2O_5$ (aq), stirred with $Na_2S_2O_5$ for 3 h, and treated with $P(OEt)_3$. After careful acidic work up (2 N HCl) under cooling (0°C), the organic layer was washed with 2 N HCl (100 mL), careful washed with a saturated $NaHCO_3$ solution (gas evolution) and brine (100 ml), dried ($MgSO_4$), and concentrated under reduced pressure. Ratio S_N2' : S_N2 = 70 : 30 (^{1}H NMR). Distillation of the crude material under standard conditions afforded racemic **6.1** as a very pale pink oil (25%).

Synthesis of N-(trimethylacetyl)-2-pyrrolidinemethanol (6.10)

To a cooled (0°C) solution of **6.9** (1.53 g, 15 mmol), triethylamine, (2.34 mL, 16.5 mmol) and a micro spatula-tip full with DMAP[1] (ca. 20 mg), in CH_2Cl_2 (12 mL), was added dropwise a solution of pivaloyl chloride (1.83 g, 15.2 mmol) in CH_2Cl_2 (30 mL) over a period of 1h. The mixture was allowed to come to ambient temperature and stirred for 18 h. The reaction was quenched on dropwise addition of water (75 mL). The water layer was extracted with CH_2Cl_2 (2 x 75 mL) and the combined organic layers were washed with brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give **6.10** (96%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.24 (s, 9 H), 1.81 - 2.07 (m, 4 H), 3.36 - 3.85 (m, 4 H), 4.27 - 4.30 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 25.4 (t), 27.3 (t), 27.5 (q), 39.1 (s), 48.5 (t), 62.3 (d), 67.6 (t), 179.1 (s).

Synthesis of N-(trimethylacetyl)-2-(2-naphthylthio)-pyrrolidine (6.11)

Methanesulphonyl chloride (0.31 mL, 4.1 mmol) was added dropwise to a stirred solution of **6.10** (689 mg, 3.72 mmol) and triethylamine (0.6 mL, 4.1 mmol) in THF (30 mL) at 0°C. Stirring was continued at 0°C for 2 h, after which time the reaction was treated in one portion with a freshly prepared mixture of 2-naphthalenethiol (595 mg, 3.72 mmol) and KO^{t}Bu (1.04 g, 9.30 mmol) in THF (20 mL) at 0°C. The mixture was stirred for an additional 2 h at 0°C. The reaction mixture was concentrated and shaken with 15% NaOH and benzene (75 mL). The aqueous layer was extracted twice with benzene (50 mL) and the combined organic layers were washed with a saturated NH_4Cl solution, dried (Na_2SO_4) and concentrated under reduced pressure to give **6.11** (53%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.21 (s, 9 H), 1.72 - 2.19 (m, 6 H), 2.90 - 3.83 (m, 3 H), 7.25 - 7.97 (m, 7 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 25.2 (t), 27.5 (q), 28.1 (t), 35.1 (t), 48.5 (t), 58.2 (d), 125.3 (d), 125.8 (d), 126.3 (d), 126.6 (d), 127.1 (d), 127.6 (d), 128.3 (d), 131.5 (s), 133.8 (s), 133.9 (s).

Synthesis of $Me_2Ti(OiPr)_3Cl$ (typical procedure)

[1] DMAP is an acronym for 4-dimethylaminopyridine, which is used as a hypernucleophilic acylation catalyst.

To a cooled (–70°C) solution of $ClTi(OiPr)_3$ (1 M in hexane, 1.5 mL, 1.5 mmol) was added a solution of MeLi•LiCl (1.59 M in Et_2O, 1.9 mL, 3.0 mmol).

S_N2' reactions with methyltitanate reagents on cinnamyl compounds (6.2)
[*ligand - catalyst combination*]:

***Without $Cu^{(I)}$ catalyst*:** To a cooled (–70°C) solution of $Me_2Ti(OiPr)_3Cl$ (1.5 mmol, see *typical procedure*) was added **6.2a** (176 mg, 1.0 mmol).The reaction mixture was stirred for 18 h during which time the mixture was allowed to come to ambient temperature. The reaction mixture was hydrolysed by hexane, saturated with water and dried ($MgSO_4$). Standard work up afforded 430 mg crude material. ^1H NMR (200 MHz) and ^{13}C NMR (50.3 MHz) data showed that the product was starting material together with unidentified impurities. No **6.1** could be detected (GC).

[L-*2-Dimethylamino-2-methyl-1-diphenylphosphino-2-phenylethane (3.9b) - CuCN•2LiCl*]: To a cooled (–30°C) solution of CuCN•2LiCl (1.0 M in THF, 0.08 mL, 0.08 mmol) was added **3.9b** (52 mg, 0.15 mmol) in THF (1 mL).The resulting mixture was stirred for 15 min. and transferred to the cooled (–70°C) solution of $Me_2Ti(OiPr)_3Cl$ (1.5 mmol, see *typical procedure*). The reaction mixture was allowed to come to ambient temperature, and cooled (–70°C) again. To the resulting clear bright yellow solution was added a solution of **6.2c** (1.53 mg, 1.0 mmol) in THF (1 mL). The reaction mixture was stirred for 18 h during which time the mixture was allowed to come to ambient temperature. The reaction mixture was hydrolysed by hexane, saturated with water and dried ($MgSO_4$). The standard work up led to **6.1** (71%) as a racemate (GC, Lipodex C).

[*N-(Trimethylacetyl)-2-(2-naphthylthio)-pyrrolidine (6.11) - CuCN•2LiCl*]: To a cooled (–70°C) solution of $Me_2Ti(OiPr)_3Cl$ (1.5 mmol, see *typical procedure*) was added a previously prepared mixture of CuCN•2LiCl (8 mol%) and **6.11** (16 mol%) in THF (1 mL). The resulting clear bright yellow solution was allowed to come to ambient temperature. After cooling (–70°C),

6.2a (176 mg, 1.0 mmol) was added. The reaction mixture was stirred for 18 h during which time the mixture was allowed to come to ambient temperature. The reaction mixture was hydrolysed by hexane, saturated with water and dried ($MgSO_4$). The standard work up led to **6.1** (70%) as a racemate (GC, Lipodex C).

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